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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/21/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/606,133	FORTINA ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2006 and 30 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 June 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0604*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is responsive to the Traversal and Request for Reconsideration of Requirement for Restriction filed June 13, 2006 and the Response to Notice of Non-Compliant Response and Statement of Substance of Interview filed September 20, 2006. With regard to the Statement of Substance of Interview, the examiner has reviewed the statement and found it to be complete and accurate. Applicants' traversal and responses regarding the Election/Restriction Requirement of March 13, 2006 are addressed below.

Election/Restrictions

2. Applicant's election with traverse of the genetic alteration of deletion in the replies filed on June 13, 2006 and September 20, 2006 is acknowledged. Upon further consideration, the requirement is hereby modified. The examiner has considered applicants' arguments and concurs that the species encompassed by the claims are drawn to related subject matter and are sufficiently related to one another that restriction of the claims to a single species is not proper. Applicants' election will be treated as an election of species.

The grounds for the election of species requirement are as follows.

This application contains claims directed to the following patentably distinct species: the multitude of different "genetic alterations" and combinations thereof set forth in the claims; see, specifically, claim 2, reciting the inversion, deletion, duplication and insertion of nucleotides, as well as claims 4-5 and 8, encompassing the "single copy loss" of numerous different single nucleotide polymorphisms and combinations

thereof. The species are independent or distinct because each such "genetic alteration" or combination of alterations possesses different structural and functional characteristics. The combinations are not, e.g., obvious variants that may be substituted one for the other, and a reference teaching one such alteration or combination would not necessarily anticipate or render obvious another such alteration or combination. Thus, the detection of each such genetic alteration/combination constitutes a distinct invention. Further, a search of more than one such alteration/combination would impose a serious burden, as each alteration/combination would require a search for a molecule with a different sequence and structure. Finally, while the species share a common asserted utility, the species do not share a substantial structural feature (as discussed above), and therefore lack unity of invention with one another (see MPEP 803.02), such that a requirement for a species election is proper.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 1 and 6 are generic.

It is noted that applicant has elected the genetic alteration of deletion (as discussed above), and has identified claims 1-8 as readable on the elected invention.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which depend from or otherwise require all the limitations of an allowable generic claim as provided by 37 CFR 1.141. If claims are added after

the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Applicants' arguments that examination of all claimed species would not pose a serious burden is relevant to the modified requirement set forth above, and has therefore been considered. The response argues that the claims "are drawn to closely related subject matter and the examination of claims 1-8 together cannot be reasonably regarded as imposing a 'serious burden' on the Examiner" (see page 3 of the Remarks of June 13, 2006). This argument has been thoroughly considered but is not persuasive. For the reasons noted above (e.g., the requirement that molecules having different sequences and different structural features be searched with regard to each species), a search of more than one species would in fact be burdensome.

As the restriction requirement has been modified, the requirement is not made final at this time. Any further traversal of or response to this modified requirement will be addressed in the next Office action, at which time the modified requirement may be made final.

3. Non-elected species other than the elected species of "deletion" are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on June 13, 2006. It is noted that claims reciting species have been examined with regard to the elected species of deletion, while applicants' generic claims have been examined with regard to their full scope.

Priority

4. It is noted that as the claimed invention is disclosed in provisional application 60/391,515, the effective filing date of the instant application is June 25, 2002.

Claim Rejections - 35 USC § 112, second paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5 are indefinite because it is not clear how the recited method steps result in "determining the presence or absence of at least one genetic alteration in a target nucleic acid for the diagnosis and management of malignant disease," as set forth in the preamble of claim 1. The claimed method includes steps of providing a target nucleic acid and "assessing said target nucleic for the extent of loss of heterozygosity relative to predetermined loci, increased loss of heterozygosity, being correlated with enhanced tumor invasiveness and metastasis." The recited method steps make no reference to "determining the presence or absence of at least one genetic alteration" or to diagnosis and/or management of malignant disease. Thus, it is not clear how or whether the recited steps actually result in achieving these effects.

Claims 1-5 are indefinite over the recitation of the limitation "said target nucleic acid having a predetermined sequence in the normal population" in step a) of claim 1. Particularly, the term "predetermined sequence" is unclear. Neither the specification nor

the prior art provide a clear definition for this terminology, and it is not clear whether the use of this term merely sets forth an inherent property of the "sequence in the normal population," or whether this language indicates, e.g., that prior steps have been taken to determine said sequence.

Claims 1-5 are indefinite over the recitation of the limitation "assessing said target nucleic for the extent of loss of heterozygosity relative to predetermined loci, increased loss of heterozygosity, being correlated with enhanced tumor invasiveness and metastasis" in step (b) of claim 1. First, it is not clear what is encompassed by the language "relative to predetermined loci;" for example, would any nucleotide or marker known to be present at a particular location (in a gene, in a chromosome, etc.) constitute a "predetermined" locus, or does this language suggest a further limitation on the types of loci encompassed by the claims? Further, the recitation "increased loss of heterozygosity, being correlated with enhanced tumor invasiveness and metastasis" is unclear; does this language limit the claims to loss of heterozygosity (LOH) that is known to be "correlated with enhanced tumor invasiveness and metastasis," or is the language indicative that any LOH detected is "correlated with enhanced tumor invasiveness and metastasis?" This language does not convey to one skilled in the art what would and would not be encompassed by the claims, such that the metes and bounds of the claims are extremely unclear.

Claim 2 is unclear over the recitation of the limitation "said genetic alteration is selected from the group consisting of inversion, deletion, duplication, and insertion of at least one nucleotide in said sequence." It is noted that the only sequence set forth in

claim 1 is the "predetermined sequence in the normal population." Thus, claim 2, in referencing "said sequence," appears to require a genetic alteration of this normal sequence (as opposed to, e.g., an alteration in the "target nucleic acid" relative to the sequence "in the normal population." Clarification is required.

Claim 3 is indefinite over the recitation of the limitation "wherein said target nucleic acid is assessed for genetic alterations...." It is noted that claim 1 includes a step of "assessing....for the extent of" LOH, but not a step of assessing for genetic alterations. It is unclear whether claim 3 requires an additional step of "assessing for genetic alteration," or whether the claim is intended to further limit the "assessing" step of claim 1.

Claims 4-5 are indefinite over the recitation of the limitation "said malignancy" in claim 4 because there is insufficient antecedent basis for this limitation in the claims. The claims are also indefinite over the recitation "said genetic alteration" because claim 4 refers to "at least one genetic alteration" but not to a single, particular "genetic alteration." It is therefore not clear whether the recitation "said genetic alteration" would further limit any alteration of the claims, or whether the limitation could apply to one of a group of alterations encompassed thereby.

Claims 4-5 are indefinite over the recitation of the limitation "said loss being associated with increased metastasis and poor prognosis" in claim 4. Does this language limit the claims to a loss that is known to be "associated with increased metastasis and poor prognosis," or is the language indicative that any loss detected is to be considered "associated with increased metastasis and poor prognosis?" This

language does not convey to one skilled in the art what would and would not be encompassed by the claims, such that the metes and bounds of the claims are unclear.

Claim 5 is indefinite over the recitation of the limitation "said single nucleotide polymorphism comprises at least one of the single nucleotide polymorphisms set forth in Figure 12." It is noted that claim 4 refers to "a single nucleotide polymorphism at the 1p36.3 region of chromosome 1," and that no other SNPs are set forth in the claims from which claim 5 depends. However, Figure 12 sets forth SNPs at multiple chromosomal locations (as opposed to only SNPs found at 1p36.3). Thus, it is not clear what SNPs are encompassed by the claims, and whether claim 5 further is actually further limiting with regard to claim 4 (as is required of a dependent claim). Further, the recitation of the limitation "at least one of the single nucleotide polymorphisms set forth in Figure 12" renders the claim indefinite because it is not clear how one would determine that a particular SNP met this claim limitation. For example, would any SNP present at a chromosomal location set forth in the Figure and having the recited bases meet the requirement of the claim, or would additional sequence features from one or more of the recited databases be required? If the latter, how would a skilled artisan known what additional information would be sufficient to establish that a particular SNP is one "set forth in Figure 12?" Would one need access to further information regarding Orchid Marker IDs and/or TSC#s? With regard to rs numbers, what information present in a dbSNP rs entry would be required to establish that a particular SNP meets the claim? The reference to Figure 12 in the claim renders its metes and bounds extremely unclear.

Claims 6-8 are indefinite because it is not clear how the recited method steps result in "determining the presence or absence of at least one specific nucleotide in a target nucleic acid for the diagnosis and management of malignant disease," as set forth in the preamble of claim 6. None of the method steps of the claim refer to or require "determining the presence or absence of at least one specific nucleotide" or to diagnosis and/or management of malignant disease. Thus, it is not clear how or whether the recited steps actually result in achieving these effects.

Claims 6-8 are indefinite over the recitation of the limitation "in a single stranded form" in step (a) of claim 6, because it is unclear from the language of the claim whether this limitation refers back to the recited "chromosomal region" or to the recited "target nucleic acid polymer," such that the requirements of step (a) are unclear.

Claims 6-8 are indefinite over the recitation of the limitations "the defined site" and "the specific nucleotide at the defined site" in step (b), "the hybridized nucleic acid polymer" in step (c), "the polymerization mixture of step (c)" in step (d), and "said at least one single nucleotide loci" in step (e) because there is insufficient antecedent basis for these limitations in the claims. It is noted that steps (c) and (d) also make reference to "the specific nucleotide at the defined site" (subsequent to the use of this language in step (b)).

Claims 6-8 are indefinite over the recitation of the limitation "assessing said target nucleic acid for loss of heterozygosity at said at least one single nucleotide loci, the degree of loss of heterozygosity being correlatable with increased tumor invasiveness and poor patient prognosis" in step (e) of claim 6. First, as previously

mentioned, the recitation "said at least one single nucleotide loci" lacks antecedent basis; further, the term "loss of heterozygosity" is employed for the first time in step (e) (the final step) of the claimed method. The language of step (e) does not make clear how this step relates either to the prior method steps of the claim or to the requirements of the preamble (as was previously discussed). Is loss of heterozygosity assessed using information gathered via the prior method steps (and if so, how)? How does this assessment contribute to "diagnosis and management of malignant disease?" The language the degree of loss of heterozygosity being correlatable with increased tumor invasiveness and poor patient prognosis" is also unclear. Does this recitation limit the claims to LOH known to be "correlatable with increased tumor invasiveness and poor patient prognosis," or, alternatively, indicate that any LOH detected is "correlatable with increased tumor invasiveness and poor patient prognosis?" Clarification is required.

Claim 7 is indefinite over the recitation of the limitation "the chromosomal region of step b) which lacks genetic alterations associated with cancer" because there is insufficient antecedent basis for this limitation in the claims.

Claim 8 is indefinite over the recitation of the limitations "said malignancy" and "said genetic alteration" because there is insufficient antecedent basis for these limitation in the claims.

Claim 8 is indefinite over the recitation of the limitation "said loss being associated with increased metastasis and poor prognosis." Does this language limit the claims to a loss that is known to be "associated with increased metastasis and poor prognosis," or is the language indicative that any loss detected is to be considered

"associated with increased metastasis and poor prognosis?" This language does not convey to one skilled in the art what would and would not be encompassed by the claim, such that the metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 112, first paragraph - enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods in which genetic alterations and/or losses of heterozygosity that are known to correlate with tumor invasiveness, metastasis, and/or poor prognosis with regard to a type or types of malignant disease in a type or types of patients are assessed to achieve the objective of "diagnosis and management" of that particular type or types of malignant disease in that particular type or types of patients, does not reasonably provide enablement for methods in which any detected genetic alterations and/or loss of heterozygosity (LOH) is considered to correlate with tumor invasiveness, metastasis and/or poor prognosis so as to accomplish "diagnosis and management" of any type of malignant disease in any type of patient, as set forth in the present claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is first noted that, as set forth above, the instant claims are unclear with regard to whether they are limited to instances in which loss of heterozygosity (LOH) is known

to be "correlated with enhanced tumor invasiveness and metastasis" (claims 1-5) or "correlatable with increased tumor invasiveness and poor patient prognosis" (claims 6-8), or whether the claims encompass methods in which any LOH detected is considered to be "correlated with enhanced tumor invasiveness and metastasis" (claims 1-5) or "correlatable with increased tumor invasiveness and poor patient prognosis" (claims 6-8)(see rejections under 35 USC 112, second paragraph set forth above). Further, regardless of whether the claims are or are not limited in such a manner, the claims clearly encompass the "diagnosis and management" of any type of malignant disease in any type of patient, as discussed in greater detail below. It is also noted that while applicants have elected the species of "deletion," the enablement of applicants' claims is considered with regard to their full scope.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (MPEP 2164.01(a)).

The claims are drawn to methods for determining the presence or absence of "at least one genetic alteration" (claims 1-5)/ or "at least one specific nucleotide" (claims 6-

8) in a target nucleic acid "for the diagnosis and management of malignant disease." Claims 1-5 encompass methods comprising "providing a target nucleic acid from a patient sample, said target nucleic acid having a predetermined sequence in the normal population" and "assessing said target nucleic acid for the loss of heterozygosity relative to predetermined loci, increased LOH, being correlated with enhanced tumor invasiveness and metastasis." Claims 6-8 encompass methods in which a target nucleic acid "from a chromosomal region known to be associated with malignancy in single stranded form" is provided and hybridized with one or more primers in which "the 3' end of the primer binds to a nucleotide flanking the specific nucleotide at the defined site in the target nucleic acid," followed by exposure of hybrids to a polymerization agent in the presence of at least one labeled deoxynucleotide and one or more chain terminating nucleotide analogues so as to form a detectable primer extension product if the "specific nucleotide" is present, analysis for the presence of said extension product, and assessment of "said target nucleic acid for LOH at said at least one single nucleotide loci, the degree of LOH being correlatable with increased tumor invasiveness and poor patient prognosis."

The teachings of the specification pertain to genetic alterations associated with a particular malignancy, neuroblastoma, in human patients (see entire specification). With regard to chromosomal location 1p36.3, the specification states that "Several investigators...have documented a strong correlation of 1 p LOH with high-risk clinical and biological prognostic variables indicating that 1p allelic deletion occurs in the more malignant subset of neuroblastomas" (p. 7). The specification also states that

"disruption of an 11q gene may predispose to the development of neuroblastoma" (p. 7) and that "allelic deletion at chromosome bands 11q23 and 14q32 may define a unique subset of human neuroblastomas that have an aggressive clinical behavior in the absence of MYCN amplification" (p. 7). The specification teaches that the "array based SNE assay" of the invention "may be used to assess the location and degree of SNPs in genes associated with oncogenesis in patients with cancer," and that it "may be used for example to assess different chromosomal regions (e.g., 1p36, 11q23 and 14q32) in pediatric patients with neuroblastoma" (p. 8). The specification asserts that "Gain or loss of genetic material at each locus correlates with tumor aggressiveness and patient outcome" (p. 8). The specification also asserts that "gain or loss of genetic material (copy number change) at each locus [of Figure 1] correlates with tumor aggressiveness and patient outcome" (p. 25). However, the examples provided in the specification are limited to the mapping of SNPs at 1p36 and 16p (see pages 22-25 and Figures 11-12). Following an assay for identification of "informative SNPs" at 1p36 using neuroblastoma cell lines (see page 26), the specification discloses that an analysis of samples from one neuroblastoma patient resulted in the identification of 5 informative SNPs that exhibited hemizygous deletion (see pages 26-27 and Figure 10). The identities of these informative SNPs are not provided in the specification. The specification also describes how the SNE assay could be applied to other neuroblastoma associated regions (p. 27-29), without in fact exemplifying such further analysis.

It is unpredictable as to whether one of skill in the art could use applicants' invention in a manner reasonably commensurate with the claims. First, with regard to

embodiments of the claimed invention pertaining to SNPs at 1p36.3 and neuroblastoma diagnosis, applicants' exemplify the identification of 5 "informative SNPs" at 1p36.3, but the identities of those SNPs which were found to be informative is not provided in the specification. Thus, one of skill in the art would not know which of the dozens of SNPs disclosed by applicant could be employed successfully in applicants' invention. Further, it is noted that the invention as claimed encompasses the use of any of the SNPs disclosed by applicants in the practice of their invention, despite the fact that the specification teaches that only few of such SNPs would be useful in neuroblastoma diagnosis. Regarding Figure 12, the Figure discloses not only a large number of SNPs at 1p36.3, but a large number at a different chromosomal location, none of which were described by applicants as having been found to be useful in neuroblastoma diagnosis. The Figure also sets forth a variety of information (locations, "bases detected," multiple databases and identification numbers), but there is no indication in the claims regarding what information is required to identify a SNP so as to allow for the practice of the claimed invention. For example, what extent of sequence information and/or what particular sequences must be identified so as to practice the claimed invention? Further, the specification exemplifies the identification of "informative SNPs" in only a single patient. The specification provides no evidence that the informative SNPs identified in this patient are or were found in additional patients or in a particular group of patients, that this patient is representative of a particular group, etc. Given that applicants' data is limited to a single patient, it is unpredictable whether informative SNPs found in this patient (even if identified) would be useful in, e.g., diagnosing

neuroblastoma or determining neuroblastoma prognosis even in a subset of the patients encompassed by the claims (e.g., human patients). Regarding LOH at 1p36.3 in human neuroblastoma in general, it is noted that the teachings of the prior art as exemplified by Maris et al (Medical and Pediatric Oncology 36(1):32-36 [1/2001]); see rejection under 35 USC 102(b) set forth below) do support applicants' assertion that detection of LOH at 1p36.3 allows one to reach conclusions regarding neuroblastoma diagnosis, invasiveness, and prognosis in humans. However, neither the teachings of the specification nor the teachings of the prior art provide adequate guidance with regard to what SNPs at 1p36.3 are informative with regard to such conclusions. Given the high skill level of one skilled in the relevant art, and the routine nature of assays directed, e.g., at SNP identification, one of skill in the art could clearly conduct further experimentation aimed at determining what SNP or SNPs at 1p36.3 (if any) may be used to accurately determine neuroblastoma prognosis, diagnosis, invasiveness, etc. However, the outcome of such experimentation cannot be predicted, and as it is unknown whether such experiments would even result in the identification of a SNP or SNPs having such properties, it clearly would require undue experimentation to use applicants' invention as claimed.

Further, applicants' claims are not limited to the methods discussed above (i.e., to methods employing 1p36.3 SNPs in diagnosing neuroblastoma in human patients), but rather encompass the diagnosis of "malignant disease" in any type of patient based on the detection of LOH in any type of target nucleic acid (see, e.g., claim 1). Claims 1-3 encompass correlating LOH of any amount or type in any gene or at any

chromosomal location with "enhanced tumor invasiveness and metastasis," and further recite that any such assessment of increased LOH allow for "the diagnosis and management" of any type of malignant disease in any type of patient. Claims 6-7 encompass methods in which any degree of LOH of any type in any gene or at any chromosomal location is "correlatable with increased tumor invasiveness and poor patient prognosis," and further encompass methods in which any LOH in any target nucleic acid "known to be associated with malignancy" allows for "the diagnosis and management" of any type of malignant disease in any type of patient. As discussed above, the teachings of the specification are limited to neuroblastoma in humans and a few particular chromosomal locations; thus, the specification is silent with regard to the vast majority of embodiments encompassed by the claims. Lacking teachings in the specification, one of skill in the art may look to the prior art for further guidance and information. In the instant case, the prior art as exemplified by Wada (Journal of Hepato-Biliary-Pancreatic Surgery 9(1):76-85 [2/2002]) provides evidence that, in instances when a known correlation exists between LOH in a particular gene or at a particular chromosomal location and a particular cancer type in a patient population, one of skill in the art may assess such LOH so as to diagnose or manage said cancer. However, the instant claims are not limited to instances in which such a known correlation exists, but rather encompass methods in which any LOH detected in any gene or location in any type of patient may be treated as an indicator of any type of cancer. Neither the teachings of the specification nor of the prior art enable the claimed methods as they are broadly claimed. Even with regard to the other chromosomal

locations asserted by applicants to be correlated with neuroblastoma aggressiveness and patient prognosis (see discussion above, regarding, for example, Figure 1 and pages 7-8 of the specification), neither the specification nor the prior art provide evidence that such correlations actually exist. Again, while further experimentation could be conducted to determine, e.g., additional instances in which LOH in a particular gene or location may be used to accurately predict, e.g., prognosis or invasiveness of a specific cancer type in a particular patient population, the results of such experiments cannot be predicted, and thus it is unpredictable as to whether one skilled in the art could practice the vast majority of the embodiments encompassed by applicants' claims.

With further respect to dependent claim 4, it is again noted that while the claim further requires that "said malignancy is neuroblastoma" and that "said genetic alteration is a single copy loss of a single nucleotide polymorphism at the 1p36.3 region of chromosome 1," this language encompasses correlating any increased LOH at this chromosomal location with "enhanced tumor invasiveness and metastasis." While dependent claim 5 further requires any polymorphism "set forth in Figure 12" or any combination thereof, any such polymorphism or combination must also correlate with "enhanced tumor invasiveness and metastasis" in order for the claim to be enabled. Claims 4-5 also each further require that any such assessment of increased LOH allow for "the diagnosis and management" of neuroblastoma in any type of patient. It is also noted that claim 5 as written encompasses a variety of polymorphisms not located at 1p36.3, despite the fact that claim 4 (from which claim 5 depends) sets forth a claim

limitation to the "1p36.3 region" (see, e.g., Figure 12B). With further regard to claim 8, while the claim requires that "said malignancy is neuroblastoma" and that "said genetic alteration is a single copy loss of a single nucleotide polymorphism at the 1p36.3 region of chromosome 1," this language encompasses correlating any single copy loss at this chromosomal location with "increased tumor invasiveness," increased metastasis, and poor prognosis, and encompasses methods in which any such loss allows for "the diagnosis and management" of neuroblastoma in any type of patient. As discussed above, the teachings of the specification and of the art also fail to enable these claims.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Maris et al (Medical and Pediatric Oncology 36(1):32-36 [1/2001]).

Maris et al disclose methods in which LOH is detected at 1p36.3 in tumor specimens from neuroblastoma patients (see entire reference). The tumor samples employed by Maris et al comprise target nucleic acids, and it is an inherent property of such nucleic acids that they have "a predetermined sequence in the normal population," as required by the claims (see page 33). Further, LOH is assessed at "predetermined loci" (see, e.g., Table 1), and Maris et al teach that LOH was found to be "highly

correlated with the presence of adverse prognostic features" (see page 34). Maris et al also teach that 1p36 LOH status was found to be "predictive of decreased event-free survival" (see pages 34-35). It is also noted that Maris et al state that "there may be clinical benefit in the early identification of" patients with 1p36 LOH "either for increased surveillance and/or adjuvant chemotherapy" (see pages 35-36). Maris et al therefore teach a method that achieves the intended use of "diagnosis and management of malignant disease" (see MPEP 2111.02 II). Regarding claim 2 and the elected species of "deletion," the method of Maris et al detects deletions at 1p36.3 (see, e.g., the discussion on page 32 of the reference). Regarding claim 3, the PCR method disclosed by Maris et al employs primers that differentiate between alleles and results in quantitation of the amounts of different alleles present, particularly as they are relevant to one another (see page 33). Accordingly, Maris et al anticipate claims 1-3.

11. Claims 1-3 are rejected under 35 U.S.C. 102(a) as being anticipated by Wada (Journal of Hepato-Biliary-Pancreatic Surgery 9(1):76-85 [2/2002]).

Wada discloses methods in which LOH of the p53 gene was assayed in tumors from pancreatic cancer patients (see entire reference). The tumor samples employed by Wada comprise target nucleic acids, and it is an inherent property of such nucleic acids that they have "a predetermined sequence in the normal population," as required by the claims (see page 77). Further, LOH is assessed at "predetermined loci" (see, e.g., Table 1), and Wada teach that p53 LOH was found to be associated with tumor invasiveness and malignant progression (see pages 82-83). Wada teaches that the differences in genetic background that they have detected, including LOH at p53, "are

implicit in the correct prognosis" for intraductal papillary-mucinous tumors of the pancreas (see page 83). Wada therefore teaches a method that achieves the intended use of "diagnosis and management of malignant disease" (see MPEP 2111.02 II). Regarding claim 2 and the elected species of "deletion," it is an inherent property of the method of Wada that it detects p53 deletions. Regarding claim 3, the PCR method disclosed by Wada employs primers that differentiate between alleles and results in quantitation of the amounts of different alleles present, particularly as they are relevant to one another (see page 78). Accordingly, Wada anticipates claims 1-3.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 6-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wada (Journal of Hepato-Biliary-Pancreatic Surgery 9(1):76-85 [2/2002]) in view of Lapidus (US 2002/0001800 A1 [1/2002; filed 6/1999]).

It is first noted that the claims as written do not require detection of any particular SNP or SNPs or the knowledge of a cancer association with regard to any SNP or SNPs; rather, the claims encompass the detection of the presence or absence of any "at least one specific nucleotide" and assessment of a target nucleic acid for LOH at "at least one single nucleotide loci" (see text of claim 6).

Wada discloses methods in which LOH of the p53 gene was assayed in tumors from pancreatic cancer patients (see entire reference). The tumor samples employed by Wada comprise target nucleic acids, and it is a property of such target nucleic acids comprising p53 gene sequences that they are "isolated from a chromosomal region known to be associated with malignancy in single stranded form" (see, e.g., pages 76-77, 82-83). Further, Wada teach that p53 LOH was found to be associated with tumor invasiveness and malignant progression (see pages 82-83). Wada teaches that the differences in genetic background that they have detected, including LOH at p53, "are implicit in the correct prognosis" for intraductal papillary-mucinous tumors of the pancreas (see page 83). Wada therefore teaches a method that achieves the intended use of "diagnosis and management of malignant disease" (see MPEP 2111.02 II), and further disclosed that p53 LOH is "correlatable with increased tumor invasiveness and poor patient prognosis."

Wada does not teach methods in which LOH is assessed using the steps set forth at (b)-(d) of claim 6 (i.e., hybridization of primers with the properties set forth in (b), exposure to a polymerization agent in the presence of at least one labeled deoxynucleotide and one or more chain terminating nucleotide analogues so as to form a primer extension product [as in (c)], and identifying a specific nucleotide at a defined site by analyzing products, as in (d)).

Lapidus teaches the detection of cancer associated LOH by single base extension reactions aimed at identifying SNPs (see entire reference, particularly paragraphs 14-19, 28-29, and 42), and teaches as an example polymorphisms within p53 that are known to be associated with cancer (see, e.g., paragraphs 3 and 8-10). The method steps described by Lapidus meet the limitations of steps (b)-(d) of claim 6 (see entire reference, particularly paragraphs 15, 45, 62, 73-76). Lapidus disclose that their methods are "highly-sensitive" (see paragraph 5) and that their methods "significantly reduce the labor involved in the detection of mutation (e.g., a deletion (including a loss of heterozygosity)," (see paragraph 7).

In view of the teachings of Lapidus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Wada so as to have detected p53 LOH by assaying for cancer-associated p53 polymorphisms using the single base extension technique described by Lapidus in lieu of the microsatellite marker analysis taught by Wada. As the method of Lapidus allows for the detection of LOH with respect to individual, specific polymorphisms, it would be readily apparent to one of ordinary skill in the art that the method is more

precise than that of Wada; further, Lapidus teaches that his method is highly sensitive and less labor intensive than prior art methods of detecting LOH. Thus, one of ordinary skill in the art would have been motivated to have made such a modification for the advantage of increased precision, sensitivity and efficiency in detecting LOH. Regarding claim 7, it is noted that Wada teaches the need to establish LOH relative to a control normal sample (see, e.g., Figure 2).

Drawings

15. The drawings are objected to for the following reasons:

Regarding Figure 6, inadequate margins have resulted in the truncation of the Figure;

Regarding Figures 7A-B, 8A-B, 9A-B, and 10A-B, dark background in the Figures has resulted in text that is difficult to read in the scanned documents.

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an

application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Conclusion

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Merbs et al (Annual Meeting of the Association for Research in Vision and Ophthalmology, Abstract No. 1830, May 2002) disclose methods of determining a minimal region of LOH on chromosome arm 3p associated with uveal melanomas using SNPs as markers (see entire abstract).

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Diana B. Johannsen
Primary Examiner
Art Unit 1634